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Chronic Neonatal Organotin Exposure Alters Radial-Arm Maze Performance in Adult Rats

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Chronic Neonatal Organotin Exposure Alters Radial-Arm Maze Performance in Adult Rats[1,2]

DIANE B. MILLER, DAVID A. ECKERMAN, MARTIN R. KRIGMAN AND LESTER D. GRANT

Neurobehavioral Toxicology Branch, Neurotoxicology Division, U. S. Environmental Protection Agency, Research Triangle Park, NC 27711 and The Departments of Psychology, Pathology and Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514

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Triethyltin sulfate Trimethyltin hydroxide Automated radial-arm maze Neonatal exposure
Learning and memory Behavioral toxicology

THE toxicity of tin compounds has been of interest since the early 19th century and Orfila is credited with first describing the toxicity of inorganic tin [11]. Recent interest in the toxicity of tin has centered on the neuropathological and neurobehavioral effects of the organotins, especially the structurally related trialkyltins, triethyltin (TET) and trimethyltin (TMT). Bouldin *et al*. [3] have described in detail the ultrastructural cytopathology found in both neonates and adults after chronic exposure to TET and TMT. One mg/kg of TET produced pathological changes in myelin in both adults and neonates characterized by widespread intramyelinic vacuolization. These data provide corroborative evidence for previous research indicating TET primarily damages central nervous system myelin [1]. In contrast chronic expsosure to 1.0 mg/kg of TMT resulted in selective neuronal necrosis in both adults and neonates. Tissue damage was particularly evident in the CA3 and CA4 fields of the hippocampal formation and in the pyriform cortex. Although Bouldin *et al*. [3] have described the neuropathological consequences of chronic exposure to TET and TMT during the neonatal period, data on the possible functional consequences of the exposure regime was not presented. The purpose of the present experiment was to characterize the learning-memory functioning of adult animals after chronic exposure to TET and TMT during the neonatal period.

The effects of chronic neonatal organotin exposure on learning and memory were assessed with a radial-arm maze (RAM). The RAM has received considerable attention as a paradigm for assessing learning and memory in the rodent [17]. RAM performance has also been shown to be sensitive to disruption by drugs and lesions [5, 10, 21] as well as neurotoxic insult [6,12]. In this spatial learning task the animal is required to obtain food located at the end of arms which radiate from a center platform. Optimal performance consists of selecting all still-baited arms before repeating previous choices. Rats rather quickly acquire efficient maze performance, demonstrating that the animal remembers which arms have been visited. Our version of the maze [14] is automated and easily allows accuracy and activity to be measured concurrently. An index of activity is important

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[2]Presented at the Society of Toxicology Annual Meeting, San Diego, CA, 1981.

[3]Send reprint requests to Dr. Diane B. Miller, Neurotoxicology Division (MD-74B), Health Effects Research Laboratory, U. S. Environmental Protection Agency, Research Triangle Park, NC 27711.

both because many neurotoxic compounds have been found to affect activity [18] and because changes in activity might confound RAM performance. In particular TET and TMT exposed animals have been shown to be hyperactive in a variety of test situations [17, 19, 20]. Therefore, accuracy, activity, time to complete the task, and time per correct selection (efficiency) were all used as measures of RAM performance.

METHOD

Animals and Treatement

Neonatal Long-Evans rats were obtained from our laboratory colony and were bred from stock originally obtained from Charles River Breeding Laboratory (Somerville, MA). During pregnancy the dams had free access to tap water and a pelleted rat chow (Wayne Lab-Blox®). The vivarium was maintained at 26°C with 12 hr:12hr light-dark cycle. Pups were cross-fostered on day 2 of life (birth=0) and reassigned such that each litter contained 4 males and 4 females. A dam never received more than 1 male and 1 female from her own litter. Rats were weaned at 21 days of age. On day 30 rats were separated by sex and housed 4/cage for the remainder of the study.

The organotin compounds were prepared in milk plus Tween-80® as vehicle. Mixtures of one drop Tween-80®/10 mg of agent were diluted with homogenized milk to a predefined concentration. The volume of milk used was adjusted so that 10 ml of solution contained the appropriate dose. Trimethyltin hydroxide (TMT) was obtained from Alfa-Ventron (Danvers, MA) and triethyltin sulfate (TET) was a gift from Organische Chem. Inst., Utrecht, the Netherlands. Tween-80® was obtained from Nutritional Biochemicals, Inc. (Cleveland, OH).

The litters were assigned in a random manner to a given treatment group. Rat pups received vehicle or vehicle plus 0.3 or 1.0 mg/kg of TET or 1.0 mg/kg of TMT in a volume of 0.01 ml/g of body weight from postnatal day 3–29. A dose of 1.0 mg/kg of TMT was given every other day due to the greater toxicity of this dose when administered on a daily basis (see Bouldin *et al.* [3] for details).

Rats were tested as adults for learning and memory performance. Each treatment group contained rats from at least 3 litters and an approximately equal distribution of males and females. The numbers of subjects per group were as follows: vehicle control (n=19); 0.3 mg/kg TET (n=16); 1.0 mg/kg of TET (n=16); 0.3 mg/kg TMT (n=8); and 1.0 mg/kg of TMT (n=8).

Apparatus and Testing

All animals were tested for learning-memory function in an automated RAM beginning at 180–200 days of age. The automated RAM (Fig. 1) has a center octagonal area (7.5 cm to a side and 32 cm in diameter) with 8 arms (26.0 cm long × 10.5 cm wide × 9.5 cm high) radiating from it like the spokes of a wheel. Solenoid-operated guillotine doors controlled access from the center of the maze to the arms, and the entire maze was covered with clear Plexiglas. Twenty-four LED-photodiode pairs monitored movement in the maze. An LED-photodiode pair was directly in front of the entrance to each arm, 5 cm into the arm, and in the food cup located at the end of each arm. A Gebrands feeder was also located at the end of each arm and dispensed 45 mg Noyes pellets directly into the food cup. The operation of the doors and pellet dispensers as well as the recording of the time and location of photodiode interruptions was controlled by a Northstar "Horizon" computer. The criterion for an arm selection was the following sequence of photodiode interruptions: center, arm and food cup. The RAM was located in a well-lighted 110 square foot room with distinguishing characteristics on several of the walls (e.g., window, electrical outlet). The entire maze was elevated 70 cm above the floor.

One week before testing rats were reduced to 85% of their free-feeding weight by restricting access to Purina rat chow to 1 hr daily; tap water was available ad lib in the home cage throughout the study. Testing was conducted in two phases. During the first phase each cup was initially baited with a 45 mg Noyes pellet. If the rat interrupted the photocell in the feeder cup, an additional pellet was presented for a possible total of 16 pellets per session. Once an animal was entering all the arms and consuming all the available pellets within one 10-min trial, the second phase was started. During the 8 days of the second phase, pellets were available only when the photocell in the feeder cup was interrupted, reducing the possible pellets per session to 8. Subjects were tested daily Monday through Friday. A daily trial ended when 8 correct selections were made or 10 min had elapsed.

Statistical Analyses

For behavioral measures with repeated indices data were analyzed by a multivariate general linear model [14]; when significant differences (Wilk's Criterion used throughout) were found, individual variables were analyzed by ANOVA. For tests with a single measurement such as weight and days to criterion, only ANOVAs were performed. F-values greater than those associated with the critical value at $p<0.05$ were accepted as significant. Post hoc individual comparisons were made using Duncan's Multiple Range Test.

RESULTS

The effect of neonatal organotin treatment on adult RAM performance was assessed with the following dependent variables; days to enter and eat in all 8 arms, unrepeated arm selections in the first 8 choices (accuracy), total photocell interruptions (activity), time to finish a session (time), and time per correct arm selection (efficiency).

The mean number of days to enter and eat in all arms (days to criterion) varied as a function of treatment, $F(4,51)=2.67$, $p<0.0422$. No significant sex effect or sex-by-treatment interaction was found, so data were combined for males and females (Fig. 2). The 6.0 mg/kg TET and TMT groups required significantly more days to reach criterion than the vehicle control or the 3.0 mg/kg TET and TMT groups ($p<0.05$). Thus, chronic treatment with TET or TMT during the neonatal period resulted in a significant increase in the time required to adequately perform the RAM task. In addition, a number of animals in the treated groups failed to satisfy the criterion to enter the second phase; 1 in the 0.3 TET group, 3 in the 1.0 TET group, and 2 in the 1.0 TMT group.

Phase 1

The MANOVA indicated significant effects for treatment, $F(16,162)=2.15$, $p<0.0086$; day of testing, $F(4,53)=28.73$, $p<0.0001$; and treatment × day of testing, $F(16,162)=1.90$, $p<0.0233$. Data from males and females were pooled in this and the remaining analyses since a MANOVA indicated no significant sex effect. Only data from the first and last day of

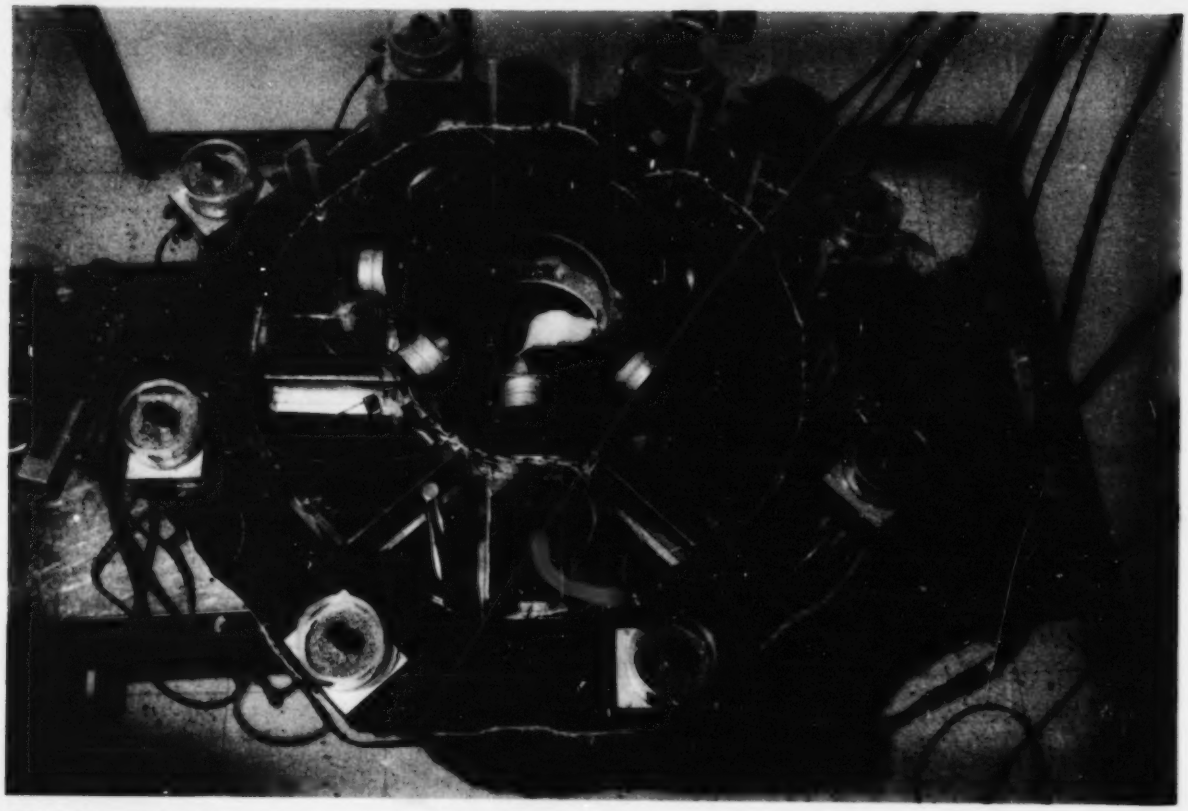

FIG. 1. Automated radial-arm maze.

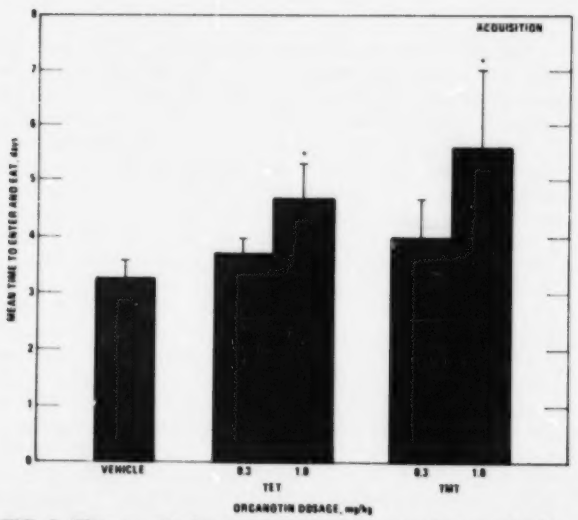

FIG. 2. Time to criterion expressed as the mean days required to enter and eat in all 8 arms of the RAM for control and organotin treated rats. Data are pooled for males and females and are presented as means ±SE. Both TET and TMT produced a dose-related increase in days required to reach criterion. *Different from vehicle control at $p<0.05$.

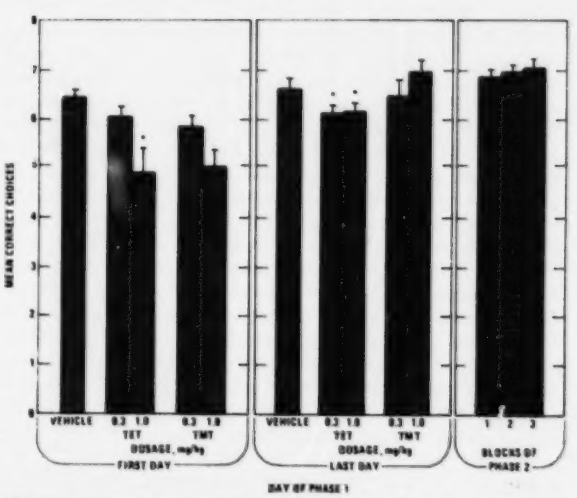

FIG. 3. Accuracy expressed as the mean number of correct selections in the first 8 arm choices for the first and last day of Phase 1 and the 3 blocks of Phase 2 as a function of dose of organotin. Data are pooled for males and females and are presented as means ±SE. The high doses of TET and TMT produced a deficit in accuracy only on the first day of Phase 1. *Different from vehicle control at $p<0.05$.

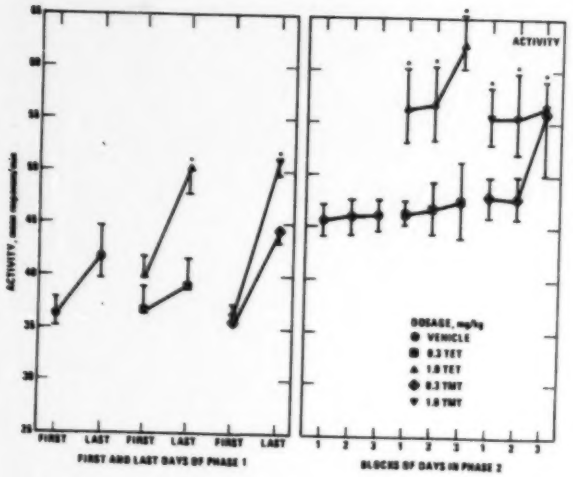

FIG. 4. Activity (photodiode interruptions) in RAM expressed as mean responses/minute for the first and last days of Phase 1 and the 3 blocks of Phase 2 as a function of dose of organotin. Data are pooled for males and females and are presented as means ± SE. *Different from vehicle control at $p<0.05$.

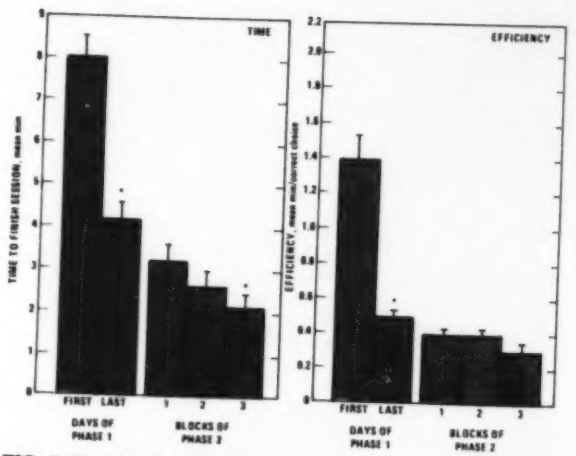

FIG. 5. Time to complete a session expressed as mean minutes and efficiency expressed as mean minutes/choice for the first and last day of Phase 1 and the 3 blocks of Phase 2 as a function of organotin dose. Data are collapsed across groups, pooled for males and females, and expressed as means ± SE. All animals required less time to complete a session and became more efficient as training progressed. *Different from the first day of Phase 1 or the 1st block of Phase 2 at $p<0.05$.

Phase 1 were included in the analyses because animals varied in the number of days they remained in Phase 1. ANOVAs indicated the measures affected by organotin treatment were accuracy and activity.

Accuracy. For the number of selections correct in the first 8 choices (Fig. 3) on the first and last day of Phase 1 there was a significant treatment, $F(4,56)=3.17$, $p<0.0091$; day of testing, $F(1,56)=17.27$, $p<0.0001$; and treatment × day of testing interaction, $F(4,56)=2.90$, $p<0.0298$. Further analysis indicated significant treatment effects for both the first, $F(4,56)=3.68$, $p<0.0099$ and final day, $F(4,56)=0.0437$ of Phase 1. On the first day of training, treated animals were significantly impaired in their ability to remember which alleys they had visited ($p<0.05$). The high dose groups for both TET and TMT made significantly less correct selections than the control or low dose groups ($p<0.05$). All groups improved as a function of training but both TET groups were still making significantly ($p<0.05$) fewer correct selections in the first 8 choices than the other groups on the final day of Phase 1. The first day differences are not due to a lower overall number of selections since there was no significant difference in the total correct choices in the session; this implies that the treated groups made more repeat selections.

Activity. Photocell interruptions per minute (Fig. 4) were used as a general index of activity in RAM. The repeated measure ANOVA on responses/minute for the first and last day of Phase 1 indicated significant treatment, $F(4,56)=3.96$, $p<0.0067$; day of testing, $F(1,56)=34.47$, $p<0.0001$; and treatment × day of testing interaction, $F(4,56)=3.10$, $p<0.0226$ effects. The groups were not significantly different in activity on the first day of Phase 1. However, by the final day of Phase 1 the groups differed significantly in activity, $F(4,56)=3.68$, $p<0.0099$. Treatment with 1.0 mg/kg of either TET or TMT produced animals which were more active than the controls ($p<0.05$) or animals treated with 0.3 mg/kg of either compound ($p<0.05$).

Time and efficiency. The repeated measures ANOVAs on time to finish the session and number of minutes/correct response indicated all groups improved with training (Fig. 5) requiring less time per session and less time per correct response. These results are reflected in the significant day of testing effect, $F(1,56)=111.3$, $p<0.0001$ for time and $F(1,56)=45.2$, $p<0.0001$ for efficiency and the nonsignificant treatment × day of testing interaction.

Phase 2

The data analysis of Phase 1 was limited to the first and last day of training because the subjects differed in the number of days required to acquire the task. However, all subjects received 8 days of Phase 2 training and rather than including only the first and last day in the analyses, the data was collapsed into blocks and all blocks included in the analyses to provide concise and complete information about performance during Phase 2. Blocks 1 and 2 are the mean of 3 days each while block 3 is the mean of the final 2 days. MANOVA indicated organotin treatment affected Phase 2 RAM performance. The MANOVA for treatment, $F(16,162)=2.50$, $p<0.0020$, and day of testing, $F(8,218)=2.62$, $p<0.0094$ was significant; but there was no significant treatment × day of testing interaction. Repeated measure ANOVAs indicated the only measure affected by treatment in this phase was activity (Fig. 4). The ANOVA on the 3 blocks of Phase 2 activity resulted in a significant treatment, $F(94,56)=4.2$, $p<0.0048$, and day of testing, $F(2,112)=4.59$, $p<0.0121$, effect but a nonsignificant treatment × day of testing interaction. All groups became more active as training progressed ($p<0.05$). More importantly, the high dose groups for both TET and TMT were significantly more active than the control or the low dose group ($p<0.05$). In addition, the low dose TET group was significantly more active than the vehicle controls ($p<0.05$). These results indicate chronic neonatal treatment with either of

these organotins produced a profound hyperactivity which was manifest throughout most of the testing.

Accuracy, time and efficiency. The repeated measure ANOVA for number of correct selections in the first 8 choices for the blocks of Phase 2 resulted in no significant main effects or interactions. These results indicated all groups were at their asymptotic level of performance by the end of Phase 1 and made no significant improvement during Phase 2 (Fig. 3). These data support the contention that the RAM is a rapidly acquired task.

The repeated measure ANOVAs for time and efficiency indicated, as does Fig. 5, that all groups became faster and required less time/correct selection as Phase 2 continued; $F(2,112)=7.8$, $p<0.0007$ for time and $F(2,112)=3.98$, $p<0.0214$ for efficiency for the day of testing variable. In neither analysis was there a significant treatment or treatment × day of testing interaction.

DISCUSSION

Chronic treatment with both trialkyltins, TET and TMT, during the neonatal period resulted in altered RAM performance in the adult. The treated animals required more days to adequately perform the task, showed a treatment decrease in accuracy, and displayed a consistent hyperactivity from the second day of testing until the end of the study.

Both TET and TMT treatment animals required more days to enter all arms and eat the available pellets. In addition, all the control animals reached criterion while there were a number of TET and TMT-treated animals that failed to ever satisfy the criterion despite several weeks of training. These time to criterion increases reflect differences in the number of pellets eaten since the groups did not differ in the total number of correct selections made even on the first day of testing. While these treatment effects may reflect motivational differences between the treated and untreated groups it is more likely a difference in the initial habituation to the RAM. The finding that neonatal organotin treatment results in an increase in days to criterion and the failure of some animals to reach criterion suggest that this measurement of habituation to RAM may serve as a useful index of neurotoxic effects. Information about other measures of habituation to the RAM is scarce since lesions or other treatments are usually administered after training (e.g., Eckermen *et al.* [5]). Consistent with the present Phase 1 control findings, Jarrard [10] reported gradually increased exploration of RAM during the initial training phase. Jarrard also reported that rats with hippocampal lesions show higher exploration levels than controls, a finding which parallels the results obtained with the organotin groups in the present study.

Reiter *et al.* [18] and Harry and Tilson [7] have determined that a single exposure to TET early in the neonatal period results in increased motor activity in the adult. The increases in activity found after TET or TMT exposure in the present study provide evidence that chronic neonatal treatment with either of these organotins will also result in increased activity in the adult. Interestingly, activity increased for all groups across days of testing although the treated groups were always more active than the control groups other than on the first day of testing. A number of investigators [2,10] have reported that limited but regular feeding resulted in increased activity in the time immediately preceeding feeding and that this effect became more pronounced with time. Also lesions of the hippocampus results in more dramatic increases as a function of limited feeding. The subjects in the present study were fed immediately following the daily session; it is likely that the activity increases across testing were related to limited food access.

TET and TMT clearly produce different neuropathological effects (see Bouldin *et al.* [3]). Yet in the present study treatment with either of the compounds on a chronic basis during the neonatal period produced the same behavioral effects, a clear hyperactivity and marginal learning-memory deficits. Treatment with either compound resulted in an increase in the number of repeated arm choices only during the early portions of testing. Although there is no previous data on the functional consequences of chronic exposure to TET or TMT during the neonatal period several studies have demonstrated that a single exposure to TET on postnatal day 5 produced a variety of neurobehavioral effects in the juvenile and adult rat. These effects included deficits in learning memory [13], changes in sensorimotor capabilities [7], increases in locomotor activity [7,18], decreases in myelin-basic proteins [15], and alteration in electrophysiological parameters such as the visual-evoked response [4,8]. Only limited data is available on the neurobehavioral effects of neonatal exposure to TMT. Miller and Dyer [12] exposed rats to TMT on postnatal day 5 and found that when tested as juveniles in the RAM these rats were not hyperactive but were less efficient than controls. Thus, the apparent absence of qualitative differences between the effects of TET and TMT observed in the present study may be related to the chronic dosing.Certainly future studies of the neurotoxicity of TET and TMT should provide a further characterization of the neurobehavioral, electrophysiological, and neurochemical effects of TET and TMT. Clearly these studies must provide a comparison of TET and TMT toxicity at different ages in chronic versus acute dosing models to allow for a truly integrated interpretation of organotin neurotoxicity.

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